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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,873	12/08/2003	Paul McGlynn	00324/US1	1167

24330 7590 02/06/2006

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EXAMINER	
PUTTLITZ, KARL J	
ART UNIT	**PAPER NUMBER**
1621	

DATE MAILED: 02/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/728,873	MCGLYNN ET AL.	
	Examiner	Art Unit	
	Karl J. Puttlitz	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *15,16 and 18-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *various*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-14 and 17, drawn to levalbuterol L-tartrate and compositions thereof classified in class 564 subclass 305+.

II. Claims 15 and 16 drawn to an inhaler classified in class 128 subclass 203.12+.

III. Claims 18-26 drawn to processes of preparing levalbuterol L-tartrate classified in class 564 subclass 305+.

IV. Claims 27-29 drawn to a method of effecting bronchodilation, classified in class 514 subclass 159+.

Inventions I and II are related as subcombinations disclosed as usable together in a single combination. The subcombinations are distinct from each other if they are shown to be separately usable. In the instant case, invention II has separate utility such as an inhaler for other aerosols. See MPEP § 806.05(d).

Inventions I and III are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the product can be made by another process, see CN 1382685.

Inventions I and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case bronchodilation can be preformed with other beta agonists.

Inventions II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions obviously have disparate functions, i.e., an apparatus vis-à-vis preparing levalbuterol L-tartrate.

Inventions II and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions obviously have disparate functions, i.e., an apparatus vis-à-vis effecting bronchodilation.

Inventions II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions obviously have different effects, preparing vis-à-vis using levalbuterol L-tartrate.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Because these inventions are distinct for the reasons given above and the search required for Groups is mutually exclusive, restriction for examination purposes as indicated is proper.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Martin Hay on 01/23/2006 a provisional election was made without traverse to prosecute the invention of Group I claims 1-14 and 17. Affirmation of this election must be made by applicant in replying to this Office action. Claims 15, 16, and 18-29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded of the rejoinder procedures set forth M.P.E.P. § 821.04.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-5 and 12-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

"The standard for determining whether the specification meets the enablement requirement [in accordance with the statute] was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See also *United States v. Telectronics, Inc.,* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the

art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.").

In the instant case, the rejected claims cover all crystalline forms or polymorphs of levalbuterol L-tartrate. Given the scope of the claims, the state of the art, and the amount of guidance in the specification, the disclosure does not contain sufficient information to enable one skilled in the pertinent art for recovery of all polymorphs of levalbuterol L-tartrate.

Specifically, the amount of guidance or direction needed to enable an invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. In the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in

pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof."

In the instant case, the state of the art of polymorph recovery is highly unpredictable. See for example *Kirk-Othmer Encyclopedia of Chemical Technology* Copyright © 2002 by John Wiley & Sons, Inc., pp. 95-147, Article Online Posting Date: August 16, 2002. This article indicates that many uncertain factors determine morphology, and specifically that the appearance of the crystalline product and its processing characteristics (such as washing and filtration) are affected by crystal habit (i.e., the general shape of a crystal). Relative growth rates of the faces of a crystal determine its shape. Faster growing faces become smaller than slower growing faces and, in the extreme case, may disappear from the crystal altogether. Growth rates depend on the presence of impurities, rates of cooling, temperature, solvent, mixing, and supersaturation. Furthermore, the importance of each of these factors may vary from one crystal face to another, see page 114.

The reference also teaches that polymorphism is a condition wherein crystalline form is intimately associated with processing ("*Polymorphism* is a condition in which chemically identical substances may crystallize into different forms. Each form is, however, only stable (thermodynamically) in a certain range of temperature and pressure. In the case of ambient pressure, eg, ammonium nitrate exhibits four changes in form between -18 and 125°C:

Transitions from one polymorphic form to another may be accompanied by changes in process conditions (temperature, pressure, shear or solution composition), transitions from one polymorphic form to another and lead to formation of a solid product with unacceptable properties (eg, melting point or dissolution rate).

A specific polymorph may be absolutely essential for a crystalline product, eg., one polymorph may have a more desirable color or greater hardness or disperse in water more easily than another polymorph.").

Finally the reference teaches that predicting crystalline form is highly unpredictable, notwithstanding recent advances ("[a] number of studies have shown that various additives can be included in a process stream to alter crystal habit. Prediction of such behavior is difficult and extensive laboratory or bench-scale experiments may be required to evaluate the effectiveness of habit modifiers. More recently, some measure of success has been achieved with altering the habit of organic crystals based on the molecular structure and forces between the crystallizing species or additive with a specific crystal face. Should an additive enhance the properties of a crystalline material, eg, by making it easier to filter, the expense associated with its use may be warranted. Significant efforts toward tailoring additives so that they have specific effects on crystal habit have been made by a number of research groups. The detailed understanding of the chemical interactions at the crystalline interface is necessary to determine the effect of additives on the crystal growth process. Chemical interactions include van der Waals, ionic, and hydrogen bonding. The influence of "tailor-made additives" on the habit of organic crystals was introduced by Lahav and co-workers and coworkers from the

Weizmann Institute, Israel in the 1980s. The reported effect for this group of additives is based on their structural similarity to the crystallizing units. The tailor-made additives are bound at preselected crystal faces and the structurally different sites that are exposed on distinct crystallographic faces. Thus the deposition of incoming crystal layers is hampered. The result is a growth rate reduction of the affected faces and a relative enlargement of its surface areas, since the slowest growing faces always dominate the crystal habit. The development of current computer software for molecular modeling or molecular simulations of crystal structures is based on Donnay and Harker and Hartman and Perdok and Hartman and Bennema approaches. Meanwhile, a number of successful operations is reported based on such computer works. Further developments are needed to save laboratory time and make faster progress in this still difficult and not finally established and understood field of crystallization. [emphasis applied]").

Even other references published after the instant invention indicate polymorph recovery is still highly experimental and unpredictable. See, for example, Rouhi, "The Right Stuff, from research and development to the clinic, getting drug crystals right is full of pitfalls", Chemical & Engineering News, February 24, 2003, pp. 32-35. Specifically, the article states that "no method yet exists to predict the polymorphs of a solid compound with significant certainty. The search for polymorphs is largely an empirical exercise. [emphasis applied]".

Accordingly, the speciation must provide sufficient disclosure regarding isolation of polymorphs in order to remedy those deficiencies of the state of the art in enabling

recovery of all crystalline forms, as recited in the rejected claims. However, the specification and the examples do not provide sufficient disclosure that would provide one of ordinary skill guidance to practice isolation of all polymorphs. Specifically, the instant specification only describes one example of crystal isolation. The specification fails to isolate more than one polymorph, much less indicate which process conditions must be used to select and isolate different crystalline forms i.e. t-butylamine. M.P.E.P. § 2164.06(b) citing "In *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), [where the court pointed to a] "limited disclosure by appellants of ...particular cyanobacterial genera operative in the claimed invention...." The claims at issue were not limited to any particular genus or species of cyanobacteria and the specification mentioned nine genera and the working examples employed one species of cyano-bacteria."

The examiner understands that there is no requirement that the specification disclose every possible embodiment if there is sufficient guidance given by knowledge in the art (See M.P.E.P. § 2164.05(a) "[t]he specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).").

However, the instant case goes beyond what is known in the art, because the state of the art for polymorph recovery is very unpredictable, and, as established above, the specification does not offer any guidance on how one of ordinary skill would go about practicing the invention for recovery of every claimed polymorph.

Accordingly, the requirement for enablement is not met since the claims go far beyond the enabling disclosure, and therefore, base on the forgoing, claims 2-5 and 12-14 are *prima facie* non-enabled for their full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a specific compound but claims 2-5 recite elements of a composition, and therefore the class of invention of claim 2-5 is unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 200278671, as evidenced by counterpart U.S. Patent Application Publication No. 2004/0101483 by Muller-Waltz et al., see attached DERWENT citation (US 483).

The rejected claims are drawn to, *inter alia*, levalbuterol L-tartrate. The rejected claims also cover those embodiments wherein: levalbuterol L-tartrate is in crystalline form; contains from 0.3 to 0.7% ethanol; is in micronized form; and is in the form of needle-like particles.

The claims also cover those embodiments covering a pharmaceutical composition, which comprises levalbuterol L-tartrate, together with a pharmaceutically acceptable carrier. The invention also covers those embodiments wherein the composition is an aerosol formulation adapted for administration using a metered dose inhaler, the aerosol formulation comprising levalbuterol L-tartrate in crystalline form and a propellant. Specific embodiments cover compositions further comprising a propellant which is 1,1,1,2-tetrafluoroethane, a surfactant, a co-solvent which is ethanol. The composition is adapted for administration using a dry powder inhaler or insufflator.

The claims also cover those embodiments comprising an aerosol formulation adapted for administration using a metered dose inhaler, the aerosol formulation comprising levalbuterol L-tartrate crystals in the form of micronized, needle-like particles, and a propellant.

With regard to the above embodiments US 483 teaches medical suspension aerosol formulations and the use of certain salts as excipients in such formulations. Specifically, the application teaches a carboxylic acid salt, selected from calcium,

magnesium and zinc salts of palmitic and stearic acid, as a solid excipient in medical suspension aerosol formulations for inhalation, comprising a pressure-liquefied, non-toxic propellant and a finely divided pharmaceutically active compound suspended in the propellant, and in particular the use of such a salt for improving the suspension stability of medical suspension aerosol formulations, for improving the metering accuracy of compressed gas packs of medical suspension aerosol formulations, for improving the valve function of the metering valve of pressurized gas packs and/or for improving the chemical stability, in particular the moisture resistance, of pharmaceutical active compounds in medical suspension aerosol formulations.

The application teaches, as a hydrofluoroalkane, (I) 1,1,1,2-tetrafluoroethane (HFA 134a) and/or 1,1,1,2,3,3,3-heptafluoro- propane (HFA 227) is particularly advantageous.

The disclosed suspension aerosol formulations contain active compounds such as levalbuterol and pharmaceutically acceptable salts and derivatives thereof. See paragraph 0017.

The application teaches that it is generally known that in the case of suspension formulations only active compound particles which are smaller than approximately 6 µm are able to enter the lungs. For the desired deposition of the active compounds in the lungs, these must therefore be pulverized or micronized before processing by means of special processes, such as, for example, pinned-disk, ball or air-jet mills. See paragraph 004.

Regarding surfactants, the application teaches that the imperfect wetting or dispersion of the active compound particles also results in these in many cases having a high proneness to adsorption and adhering to surfaces such as the container inner wall or the valve, which leads to an underdosage and to a poor metering accuracy from spray burst (puff) to spray burst. A surface-active excipient must therefore as a rule be added to suspension formulations in order to lower the adsorption on interfaces and to achieve an acceptable metering accuracy. See paragraph 005.

The application also teaches that it is proposed to leave out the surface-active excipients in HFA-containing formulations if possible or--if they are indispensable for technological reasons--to add a polar cosolvent such as, for example, ethanol in order to improve the solubility in a manner known per se and to dissolve the surface-active agents. See paragraph 007.

The difference between the compounds and compositions disclosed in US 483 and those covered by the rejected claims is that while the rejected claims cover levalbuterol L-tartrate, US 483 fails to specifically teach a tartrate salt. However, the use of tartrate as an acid addition salt for β-agonists in aerosol pharmaceuticals is commonplace in the art, as evidenced by disclosure formoterol tartrate. See, for example, paragraph 0031. Therefore, absent a showing of unexpected results, tartrate salts of levalbuterol are within the motivation of those of ordinary skill, and thus, prima facie obvious. See M.P.E.P. § 2144.09 ("A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function

entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)"). Regarding the fact that the claims specifically recite L-tartrate, stereoisomers are prima facie obvious in the absence of unexpected results. See M.P.E.P. 2144.08, citing structural similarities that have been found to support a *prima facie* case of obviousness. See, e.g., *In re May*, 574 F.2d 1082, 1093-95, 197 USPQ 601, 610-11 (CCPA 1978) (stereoisomers).

Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over CN 1382685, See Online CAPLUS citation from Chemical Abstracts, Columbus OH, USA, Abstract Number 2003:811239 (CN 685).

The rejected claims cover levalbuterol L-tartrate, in a crystalline form. In this regard, CN 685 teaches salbutamol tartrate, which has been crystallized. The drifference between levalbuterol L-tartrate as claimed and the compound disclosed by CN 685 is that the reference fails to teach the L isomer of the tartrate acid addition salt. However, in the absence of unexpected results, stereoisomers are prima facie obvious. See M.P.E.P. 2144.08, citing structural similarities that have been found to support a *prima facie* case of obviousness. See, e.g., *In re May*, 574 F.2d 1082, 1093-95, 197 USPQ 601, 610-11 (CCPA 1978) (stereoisomers).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karl J. Puttlitz whose telephone number is (571) 272-0645. The examiner can normally be reached on Monday to Friday from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter, can be reached at telephone number (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karl J. Puttlitz
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